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ELECTROLYTE DISORDERS OR PRE-ANALYTICAL VARIATIONS

Biochemistry

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ABSTRACT

Background and Objectives: The timely and accurate analysis of serum electrolytes is crucial in clinical laboratories for Acute Kidney Injury informed decisions about patient care. Delays in sample processing and storage conditions can potentially impact the results, leading to clinical implications. This study aims to investigate the effect of delayed sample processing and storage on electrolyte estimation over a specified time period. Understanding how temporal variations affect electrolyte measurements is essential for ensuring the reliability and accuracy of clinical laboratory results. **Material and methods** As per recommended protocols a10 ml whole blood sample was procured from each participant in the study and subsequently divided into four aliquots. Specifically, the 1st aliquot, comprising 4 ml, was designated for baseline value determination after processing, while the remaining three aliquots, each containing 2 ml, were labeled as the 2nd, 3rd, and 4th aliquots. The surplus serum obtained from the 1st aliquot underwent further division into three aliquots, all of which were stored at a temperature range of 2-8°C in a refrigerator. The refrigerated serum from the 1st aliquot was subjected to analysis at 24, 48, and 72 hours post-storage. Meanwhile, the whole blood samples from the 2nd, 3rd, and 4th aliquots, preserved at room temperature (23 ± 10°C), were processed and analyzed at 2, 4, and 6 hours following sample collection. The estimation of electrolytes was carried out using Ion Selective Electrodes (ISE). This comprehensive methodology allows for a detailed investigation of electrolyte levels in both refrigerated serum and whole blood samples, with assessments conducted at various time intervals. **Result and conclusion:-** We identified a statistically significant difference, with a p-value < 0.05, in the levels of K+ in whole blood stored at room temperature (RT) for 2 hours, and in serum stored for 24, 48, and 72 hours at 2-8°C. Conversely, Na+ levels remained stable in whole blood stored at RT for up to 6 hours and in stored serum at 2-8°C for up to 72 hours. It is crucial to separate and analyze samples for K+ estimation within 2 hours of collection. The accurate measurement of electrolytes is essential for the effective treatment and improved prognosis of critically ill patients. Achieving this requires meticulous management of the preanalytical phase through the implementation of a standardized protocol in both the laboratory and sample processing

KEYWORDS

Electrolyte disorders, Preanalytical variable, sodium, potassium

INTRODUCTION

Laboratories of tertiary care hospitals received over a thousand samples a day. These laboratories are facing so many challenges like a breakdown of equipment or lack of reagents or lack of staff, which can prevent same-day processing of samples. Maintaining the stability of serum analytes during sample storage is most common issue in any clinical laboratory, the temperature at which the samples are stored constitutes an important preanalytical variable that may affect analysis results in the clinical biochemistry laboratory setting.[1] The analysis of electrolytes forms a major decisive step in the diagnosis and management of the critically ill. Electrolyte abnormalities can precipitate life-threatening events by derangements in its metabolic process or as a consequence of an underlying disease. It is a general recommendation to complete the analysis of electrolytes as soon as possible, failing which the results can be inaccurate and unreliable. Testing in a laboratory is a complex interrelated process, involving preanalytical, analytical, and postanalytical phase and each phase is prone to error, thus affecting the final result.[2] Estimation of sodium and potassium is very sensitive to change in temperature, delayed centrifugation, and period of contact with clot. There is still no standard defined for the stability limits of analytes and the criteria for rejection before processing them due to the lack of standard experimental designs and wide variability in maximum permissible instability specifications.[3] Electrolytes play an important role in various physiological functions of the body. It also plays vital role in the functioning of cells, in maintaining tissue perfusion and acid-base balance. Regulation of extra and intracellular concentrations of various electrolytes is crucial for many metabolic processes and organ functions. Kidneys play an important part in maintenance of the levels of electrolytes. Besides the kidneys, the other mechanisms which are involved in the regulation of fluid and electrolyte balance in the organism are hormones like antidiuretic hormone, aldosterone, and parathyroid hormone and various other factors such as physiological stress and age also play important roles in the regulation of electrolyte balance[4].

Analysts use laboratory diagnostic for diagnosis, monitoring, and prognosis in patients. Laboratory medicine has the potential to improve patient safety since it crosses many pathways and organizational boundaries. Clinicians can implement proactive interventions to highlight high-risk situations, such as pre-assessment and drug therapy monitoring. Laboratories have a considerable role to play in diagnostic and therapeutic decision in acute kidney injury and monitoring safety. Increasing the knowledge of the use and abuse of testing, and studying the outcomes, should be part of the value-added function of laboratory services. This condition will improve the quality of care and affect the results [5]. Distinguishing between the normal and abnormal fluid balance in the patient can be challenging. The diagnosis of fluid balance abnormalities requires the informed and reasonable interpretation of clinical and laboratory data [6]. Disturbances in electrolytes are measurable by biochemical parameters in the bloodstream that determines the clinical manifestations of interactions between metabolic events such as hormones, medications, renal physiology, sepsis, hydration deficiencies, and vascular events.[7] It plays important role in protecting acid-base balance, tissue perfusion, cellular function, and the management of several clinical conditions.[8] It has been established that the prevalence of electrolyte abnormalities is directly related to mortality and increase in hospitalization period.[9] Disorders of serum sodium and potassium are common in hospitalized patients as well as in patients presenting to the emergency department [10]. The prevalence of electrolyte imbalance in the emergency department has been associated with an increased risk of mortality. Alterations in electrolytes are associated with a number of clinical conditions and prompt diagnosis of electrolyte imbalance and treatment are crucial in the management of patients admitted to the emergency department.[11,12,13], Most common electrolyte imbalances are hypo- and hyper-states of potassium, magnesium, sodium, and calcium.[14] Disorders of serum potassium and sodium have been found to be presented in more than 10% of patients and are common in outpatients.[15,16] Many factors have been found to be associated with the development of Dyskalemias and dysnatremia.[17] Hyperkalemia often is due to renal insufficiency and/or various medications (diuretics,/ angiotensin receptor blockers) whereas hypokalemia most often is a consequence of diuretic therapy.[18] Hypernatremia is mostly due to inadequate fluid therapy in critically ill patients or dehydration in ambulatory patients while hyponatremia can be a consequence of diuretic therapy, the syndrome of inadequate vasopressin secretion, or a low effective circulating volume as in cirrhosis of the liver or heart failure.[19] The association between dysnatremia and acute kidney injury onset however is anything but consistent. Both hyperkalemia and potassium variability are most likely acute kidney injury predictive. Serum calcium and acute kidney injury risk are apparently associated in a U-shaped manner. Higher phosphate levels potentially predict acute kidney injury in non-COVID-19 patients, opposing findings have however been reported from patients under dialysis therapy of established acute kidney injury.[20] Dyskalemias are also commonly

encountered in the emergency department as well as in hospitalized patients. It was recently stated that the risks of hypokalemia were probably underestimated and that they are comparable to or even larger than those of hyperkalemia [21]. Drugs are also known to cause adverse electrolyte consequences. These drugs could be anti-hypertensive agents like diuretics and drugs affecting the Renin Angiotensin System, hormones like insulin, antipsychotics or steroids [4].

In summary, In a tropical country like India where the ambient temperature can go very high, maintaining the stability of a sample if not processed immediately can be a big deterrent in the accuracy of the result. Also, situations like instrument breakdown, power failure, shortage of manpower, lack of awareness about the sample stability, and casual behavior of the technical staff, some tests being performed later can make the situation even worse. In such situations, the samples are left unprocessed with the sera being un separated from the clot or they are stored in the refrigerator within a temperature range of 2 to 8°C. The measurement of electrolytes at this point may not be accurate then, leading to a spurious rise or fall. The purpose of the present study was to establish the significance of electrolyte analysis and different pre-analytical variable effect on them while interoperating them for the patient treatment. There is paucity of published literature on electrolyte disorders and pre-analytical variations. With this background, this study was conducted to evaluate the impact of time delay and clot contact time of serum in the analysis of serum sodium, and potassium.

MATERIAL AND METHOD

An Analytical study was carried out at the Department of Biochemistry, Dr. Rajendra Prasad Government Medical College Kangra at Tanda, District Kangra, Himachal Pradesh, India. Sampling population was comprised of all adult subjects (both male and female) who came to the centralized collection center of the Hospital. Voluntarily willing subjects were also recruited for the study. The subjects who refused, Subjects with Chronic illness like Tuberculosis, Cancer or Immuno-compromised states, Pregnant or lactating mothers or who had either donated or received blood in last 3 days were excluded from the study. The first subject was selected by acute kidney injury the last digit of currency note and thereafter three subjects were picked by systemic random sampling on every first working day of the week. After recording demographic features, personal history; general physical examination was done of the selected subject after obtaining informed written consent on preformed Performa. 100 subjects were enrolled in the study. As per recommended standard protocol, 10 ml whole blood sample was taken from each subject of study. The blood sample was divided into four aliquots; 1st aliquot of 4ml and rest three of 2ml each were labeled as 2nd, 3rd and 4th respectively. To obtain the baseline value blood from 1st aliquot was allowed to clot for 30 minutes and then centrifuged at 2500 rpm for 10 minutes. The remaining serum of 1st aliquot was divided into three aliquots; and stored at 2- 8°C in the refrigerator. Refrigerated serum of 1st aliquot was analyzed at 24 hr, 48 hr and 72 hr of storage. Whole blood in 2nd, 3rd and 4th aliquots kept at room (23 ± 1°C) temperature was centrifuged and separated at 2 hr, 4 hr and 6 hr after sample collection and analyzed thereafter. Electrolyte estimation was done by ISE (ion selective electrodes) Serum was analyzed directly from respective aliquots after bringing them to room temperature on Easylyte supplied by Medica corporation 5, Oak Park Drive, Bedford, MA-1413, USA. Easylyte works on principle of ion selective electrodes. The analysis takes 55-60 seconds. It requires a 100µl of serum plasma or whole blood. Calibration is automatic in it or can be performed on demand. A unique solution pack contains standard solutions to calibrate the analyzer.

RESULTS AND OBSERVATION

Electrolytes were examined to assess the impact of delayed processing and storage at different temperatures. Statistical analysis was conducted using**.** Repeated measure analysis of variance was employed to measure the change in concentration over time. The significance level was set at $p < 0.05$. To validate the significance of differences in values for each analyte at various temperatures and time points in hours, Student's paired t-test was performed. A total 100 subjects were enrolled in the study, with 33 females and 67 males. Among the participants, 81 were healthy, while 19 were on medications for hypertension, diabetes mellitus, or hypothyroidism. Subjects were distributed across different age groups: 22 in the 18-30 years group, 50 in the 30-45 years group, 16 in the 45-60 years group, and 12 above 60 years old. Statistically significant differences ($p < 0.05$) were observed in K+ levels in whole blood stored at room temperature for 2 hours and in serum stored for 24, 48, and 72 hours at 2-8°C. Na+ levels remained stable in whole blood stored at room temperature for up to 6 hours and in stored serum at 2-8°C. Qualitative assessment of free hemoglobin was negative for all specimens.

Table: III effect of delayed processing and storage on Potassium estimation (N=100)

Time of analysis	Range	Mean ± Std. Deviation	P value (compared to zero hour value)
Baseline /Zero value Bld K+ 0 hour	3.80 - 5.20	4.47 ± .28	
Sample processing after = 2 hours	3.98 - 5.20	4.57 ± .27	.003
Sample processing after = 4 hours	4.00 - 5.30	4.58 ± .30	.004
Sample processing after = 6 hours	3.90 - 5.70	4.57 ± .37	.022
Serum stored for 24 hours	4.25 - 5.20	4.64 ± .26	.000
Serum stored for 48 hours	3.90 - 5.92	4.69 ± .40	.000
Serum stored for 72 hours	3.80 - 5.70	4.67 ± .38	.000

Table shows change in mean value of whole blood samples stored at room temperature for 2 hours , 4 hours and 6 hours and serum stored for 24 hours , 48 hours , and 72 hours s at 2-8°C. It further shows p value of whole blood samples stored at room temperature for 2 hours, 4 hours and 6 hours and serum stored for 24 hours, 48 hours, and 72 hours at 2-8°C compared to zero hours value. There is a statistically significant increase ($p<0.05$) in all processing delay and storage conditions.

Table VI effect of delayed processing and storage on sodium estimation.

Time of analysis	Range	Mean ± Std. Deviation	P value compared to zero hr value
Baseline /Zero value Bld K+ 0 hour	133.9 -144.3	141.2 ± 1.95	
Sample processing after 2 hours	133.9 - 144.3	141.2 ± 1.94	.147
Sample processing after + 4 hours	133.0 - 144.5	141.3 ± 2.30	.640
Sample processing after 6 hours	134.0 - 144.9	141.4 ± 2.01	.252
Serum stored for 24 hours	133.9 - 144.3	141.2 ± 2.00	.320
Serum stored for 48 hours	133.0 - 144.5	141.3 ± 2.28	.779
Serum stored for 72 hours	134.0 - 144.9	141.4 ± 1.98	.312

Table VI shows change in mean value of whole blood samples stored at room temperature for 2 hours , 4 hours and 6 hours and serum stored for 24 hours , 48 hours , and 72 hours s at 2-8°C. It further shows p value of whole blood samples stored at room temperature for 2 hours, 4 hours and 6 hours and serum stored for 24 hours, 48 hours, and 72 hours at 2-8°C compared to zero hours valueSodium values remain statistically stable n all processing and storage condition.

DISCUSSION

Fluid and electrolyte balance is crucial for understanding the maintenance of homeostasis and the successful treatment of many metabolic disorders. There are many regulatory mechanisms for electrolyte balance. Disturbances of these mechanisms lead to electrolyte imbalance, which may be a life-threatening clinical condition. Electrolyte imbalance is a common manifestation of many diseases. All electrolyte imbalances should be comprehensively considered. The examination is essential to clarify the clinical scenario for effective and successful treatment. Most electrolyte imbalances are low and high sodium, potassium, calcium, and magnesium [22]. Potassium maintains the cardiac rhythm and contributes to neuromuscular conduction. K level imbalance, indicated by hyperkalemia or hypokalemia, will cause cardiac arrhythmias and neuromuscular weakness. Kidney and endocrine disorders are usually

characterized by plasma electrolyte imbalance. Changes in electrolyte levels are associated with pathological consequences and increased mortality [23].

Statistically significant differences ($p < 0.05$) were observed in K+ levels in whole blood stored at room temperature for 2 hours and in serum stored for 24, 48, and 72 hours at 2-8°C. Na+ levels remained stable in whole blood stored at room temperature for up to 6 hours and in stored serum at 2-8°C. Previous studies have demonstrated an increase in K^+ is due to serum-cell contact at room temperature[24,25]. This study shows that with an increased delay period in analysis and clot contact time, the concentration of serum potassium increases. The increase in K+ after 24 h is most likely caused by malfunction of the Na+/K+ ATPase pump, resulting in diffusion of K+ from the erythrocytes driven by the intracellular–extracellular concentration gradient. In the cooling process, glycolysis is inhibited. Thereby Na-K ATPase-depending power cannot maintain its gradient. Consequently, intracellular potassium will exit the erythrocytes, leading to an increase in potassium levels in plasma [26]. Furthermore, storing of erythrocytes showed increased potassium leakage, and all these effects increased with increasing storage time [27]. Samples that are left without serum separation at room temperature are subjected to evaporation and failure of maintenance of sodium potassium pump leading to potassium leak from the cells. This leak is more pronounced at low temperatures at around 4°C. A phenomenon called seasonal pseudo hyperkalemia was documented where hyperkalemia was more frequent in winters when ambient transport temperature was lower than in summers.[28] Several pre-analytical variables affect electrolyte results, including the type of anticoagulant, storage conditions, and hemolysis. Hemolysis of blood causes a false increase in plasma K^+ results by releasing intracellular K^+. However, grossly hemolyzed specimens will affect the analyses of Na^+ and Cl^- levels due to a dilutional effect. The presence of excess anticoagulants when small volumes of blood are collected will similarly cause a dilutional effect and falsely decreased plasma levels of Na and Cl. Refrigeration of unseparated whole blood may enhance the intracellular release of K from erythrocytes [29]. In a study by Kachhawa et al serum sodium and potassium was stable up to 30 days, when sera are separated within 30minutes after centrifugation.[30] other stated that there is no significant change in sodium till 6 hours but it decreased significantly at 24 hours which is not consistent with the above studies.[31,32] Other researchers discovered that delayed sample-processing of over 2 (two) hours did not affect the serum sodium and chloride level. Other researcher have concluded that the storage of serum for sodium, potassium, and chloride analysis can be done at a maximum of 3 hours at a temperature of 4oC. (4). In previous study by Trisna *et al*.[33], sample-processing delays of over 2 hours do not affect the results of sodium and chloride examinations, while sample-processing delays of more than 2 hours can affect potassium results, which is in agreement with our study. Failure of sodium potassium pump can attribute to change, as sodium finds a way intra cellularly due to the concentration gradient. Since sodium density is lower than the chloride, there is only one-tenth of sodium in erythrocytes, so serum testing delays do not cause sodium leakage into the serum [34].

Various electrolyte results depended on the temperature conditions of each country. Research conducted in tropical countries will provide higher temperatures so that the stability of sodium, potassium, and chloride can change after a few hours of centrifugation. Na and Cl results are affected at 3 hours, but K results are affected at 1 hour. Climatic conditions and uncovered sample cups left under the fan for a few hours are responsible for this evaporation and falsely high serum electrolyte values[27]. Evaporation of samples could be the major cause leading to concentration of samples resulting in high values[35].

CONCLUSION:-

To conclude we suggest that the samples for measurement of serum electrolytes should be analyzed as soon as they are received in the laboratory preferably within 1-2 hour. In the event of any delay, sample cups should be properly covered and stored under proper environmental conditions to avoid erroneous results. As a result, each laboratory's guidelines should state the stability of each analyte's storage. The laboratory must follow standards of Operational Procedure for storage optimization. Ensuring the precise measurement of electrolytes is crucial for effectively treating and predicting outcomes in critically ill patients. Achieving this goal involves optimizing the preanalytical phase by adhering to a standardized protocol in laboratory practices and sample storage.

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